Int. J. Cancer: **118,** 449–452 (2006)

Personal and family history of autoimmune diabetes mellitus and susceptibility to young-adult-onset Hodgkin lymphoma

Ola Landgren[1,4]*, Magnus Björkholm[1], Scott M. Montgomery[2], Henrik Hjalgrim[3], Jan Sjöberg[1], Lynn R. Goldin[4] and Johan Askling[2]

[1]*Division of Hematology, Karolinska Hospital and Institutet, Stockholm, Sweden*
[2]*Clinical Epidemiology Unit, Department of Medicine, Karolinska Institutet, Stockholm, Sweden*
[3]*Department of Epidemiology Research, Statens Serum Institut, Copenhagen, Denmark*
[4]*Genetic Epidemiology Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, Bethesda, MD, USA*

Young-adult-onset (15–44 years of age) Hodgkin lymphoma (HL) is believed to arise as a consequence of late primary infection in susceptible individuals. The properties of this susceptibility remain little understood. We have previously reported an increased occurrence of HL in patients with rheumatoid arthritis and among their offspring, suggesting that susceptibility to autoimmunity might be of importance also in the pathogenesis of HL. To explore this hypothesis, we assessed the association of personal and family history of diabetes mellitus, with risk of subsequent HL in a population-based case-control study, including as cases all individuals diagnosed with HL above 15 years of age 1964–1999 (n=6,873) in Sweden, and matched population controls (n=12,565). First-degree relatives of cases and controls were identified through linkage with the Multi-generation Register. We identified discharges listing diabetes mellitus through linkage with the Inpatient Register (1964–2000). We used odds ratios (OR) as measures of relative risk. Cases with young-adult-onset HL were less likely to have a personal (OR=0.5, 95% CI 0.2–1.1) or family (OR=0.7, 95% CI 0.6–0.8) history of diabetes mellitus. In contrast, HL diagnosed at older ages was neither associated with a personal (OR=1.0) nor family (OR=1.0) history of diabetes mellitus. These findings suggests that characteristics of the immune system associated with conditions such as diabetes mellitus type I are of importance in the pathogenesis of young-adult-onset HL.

Key words: Hodgkin lymphoma; susceptibility; etiology; pathogenetic; autoimmune; familial; diabetes

Although young-adult-onset (15–44 years of age) Hodgkin lymphoma (HL) is thought to arise as a consequence of delayed primary infection,[1] such as Epstein-Barr virus (EBV),[2–4] late infection is not in itself a sufficient cause. Family, HLA and twin-studies indicate the existence and importance of genetic susceptibility in the etiology of HL,[5–8] but the biological properties of this susceptibility is unknown.

Inflammatory diseases of autoimmune origin describe an intriguing association with malignant lymphomas including HL.[9–12] Recently, we found a 3-fold risk of subsequent HL among patients with rheumatoid arthritis (RA) and an increased risk of childhood HL in their offspring.[12] The underlying mechanisms behind the observed associations between RA and HL remain, however, poorly understood. For instance, the increased risk of HL may be related to the underlying susceptibility towards autoimmunity that is present in individuals and families with RA, represent a more direct effect of RA-related systemic inflammation, or a combination of both. It is therefore of interest to assess the risk of HL in relation to other autoimmune diseases, in particular in autoimmune conditions with an established underlying susceptibility and familial aggregation but without systemic chronic inflammation. Diabetes mellitus type I is a prototype such condition. To explore the association between personal and familial history of diabetes mellitus type I and the risk of subsequent HL, we performed a population-based case-control study of almost 7,000 cases of HL, more than 12,000 population-controls and their linked first-degree relatives.

Subjects and methods

Cases and controls

The Swedish Cancer Register has been in operation since 1958 with a near complete coverage.[13,14] In this register, we identified as cases all individuals registered with a diagnosis of HL 1964–1999. For each case, information on date of birth, date of diagnosis of HL and sex was collected. Through the nationwide Register of Total Population, which since 1969 is the Swedish census register, we identified 2 controls for each case, matched on sex, year of birth, marital status and county of residence in the year of the index patient's HL diagnosis. After exclusion of controls themselves diagnosed with HL before their case, and cases and controls born outside Sweden, 6,873 cases and 12,565 controls remained (Table I).

Family members

The Swedish Multi-generation Register[15] includes information on parent-offspring relations for Swedish citizens born in 1932 or later. Through iterated linkage using this register, parents, siblings and offspring of individuals born 1932 or later can be identified. We identified a total of 14,160 parents, 11,255 siblings and 21,850 offspring born before the diagnosis of HL in the index case.

Diabetes mellitus

All individuals were further linked with the Swedish Inpatient Register 1964–2000,[14] which contains individual-based information on discharges from inpatient care [coded according to International Classification of Diseases (ICD) versions 7–10] with a population-based (county-wise) coverage that encompassed 50% of Sweden in the mid 1970s and 100% since 1987.[14,15] Through this linkage, we collected information on all discharges listing diabetes mellitus including date of discharge. Since there is no code that unambiguously delineates diabetes mellitus type I from type II (or from the intermediate late-onset autoimmune type), but practically all cases with diabetes mellitus type I in Swedes are diagnosed before 30 years of age, we defined *diabetes mellitus type I* as a first diabetes mellitus discharge before this age. To test the robustness of this classification, other age cut-offs (20 and 40 years of age) were also employed.

Statistics

We calculated odds ratios (OR) as measures of relative risks using conditional logistic regression. Young-adult-onset HL was defined as HL diagnosed between 15 and 44 years of age.[1]

Grant sponsor: Swedish Cancer Society; Grant number: 4537-B02-O2XBB.
***Correspondence to:** Genetic Epidemiology Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, 6120 Executive Boulevard, Bethesda, MD 20892-7236, USA. Fax: +301-402-4489.
E-mail: landgreo@mail.nih.gov
Received 8 November 2004; Accepted after revision 27 April 2005
DOI 10.1002/ijc.21347
Published online 27 July 2005 in Wiley InterScience (www.interscience.wiley.com).

Personal history of diabetes mellitus was assessed for cases and controls up until 2 years before the diagnosis of HL in the index case (to avoid reversed causality or selection bias), and was stratified according to time between the first inpatient discharge listing diabetes mellitus, and HL (1–4, 5–9, 10 or more years), sex and age at first discharge listing diabetes mellitus (0–29, 30 or more years). Family history was assessed according to type of relation (parent, sibling or offspring), and relative's age at first discharge with diabetes mellitus (0–29 and 30+ years) and timing of relative's diabetes in relation to diagnosis of HL in the index case. To adjust for possible differences in family size between cases and controls, models were adjusted for the number of identified parents, siblings and offspring. To detect any register-related bias related to the fact that for index-individuals deceased before 1990, the possibility to identify first-degree relatives in the Multi-Generation register is reduced to 50%, we performed separate analyses restricted to cases diagnosed with HL 1990–2000 and their controls (which revealed similar ORs as those based on the entire dataset).

Results

Personal history

Young-adult-onset HL was associated with a decreased occurrence of diabetes mellitus (OR=0.5, 95% CI 0.2–1.1), which was essentially made up by diabetes mellitus type I (OR=0.5, 95% CI 0.2–1.4, Table II) prior to HL. Late onset HL was neither associated with a history of diabetes mellitus overall (Table II), nor in analyses stratified by latency periods ($0.9 < OR < 1.2$) and calendar periods of HL ($0.8 < OR < 1.4$). With respect to childhood onset HL (0–14 years of age, 224 cases) no cases but 2 controls had a pre-HL diabetes discharge.

Family history

Young-adult-onset HL was associated with a reduced overall occurrence of diabetes mellitus in first-degree relatives (OR=0.7, 95% CI 0.6–0.9) (Table II), which was true for parents and siblings (irrespective of siblings age at diabetes mellitus) but not for offspring, and for diabetes mellitus type I (OR=0.7, 95% CI 0.4–1.3). In late onset HL, there was no overall association with diabetes mellitus in first-degree relatives, but diabetes mellitus was somewhat more common among parents of cases compared to controls (OR=1.5, 95% CI 1.1–2.2). All parents with a recorded history of diabetes mellitus were diagnosed at the age 30 years or above. Neither the timing of relatives' diabetes in relation to the case's HL, nor sex of the cases or controls or calendar period of HL markedly modified the ORs (data not shown). With respect to childhood onset HL, 7 cases and 23 controls had a family history of diabetes, OR=0.7, 95% CI 0.3–1.5).

TABLE I – OVERALL NUMBER OF CASES WITH HODGKIN LYMPHOMA (HL) DIAGNOSED IN SWEDEN 1964–2000 AND THEIR MATCHED CONTROLS

	Cases	Controls
Overall	6,873	12,565
Sex		
Males	3,968	7,263
Females	2,905	5,302
Age at HL		
15–44	2,581	4,693
45+	4,292	7,872
Year of HL diagnosis		
1964–1979	3,576	6,576
1980–1989	1,796	3,303
1990–2000	1,501	2,686

Discussion

The results of our population-based case-control study using data on family members and diabetes mellitus collected prospectively and independently of case-control status suggest a inverse association between diabetes mellitus type I (personal as well as familial) and young-adult-onset HL. No association was found between a personal history of diabetes mellitus and HL diagnosed after 45 years of age, but a positive association between parental history of diabetes mellitus and HL diagnosed after 45 years of age was observed. For cases with childhood onset HL (0–14 years of age) numbers were too small to provide reliable estimates.

Diabetes mellitus type I shows strong genetic susceptibility[16] on which environmental factors may exert influence[17–20] and is a prototype Th1-pattern autoimmune disease.[21] While factors like maternal age and low birth order have been linked to increased risk of diabetes mellitus type I,[22] the evidence to link diabetes mellitus type I with childhood infections or proxy markers thereof is not as strong as for young-adult-onset HL.[23] Data on the risk of HL in patients with diabetes mellitus (or *vice versa*), let alone

TABLE II – NUMBER OF EXPOSED CASES (CA) AND EXPOSED CONTROLS (CO), AND ODDS RATIOS (OR) WITH 95% CONFIDENCE INTERVALS (CI) FOR A PERSONAL AND FAMILY HISTORY OF DIABETES DEFINED AS DISCHARGE FROM INPATIENT CARE LISTING DIABETES MELLITUS UP TO 2 YEARS BEFORE THE DIAGNOSIS OF HODGKIN LYMPHOMA (HL)[1]

Diabetes	15–44 years at HL (n =2,563/4,676)[2]			45+ years at HL (n =4,292/7,872)[2]		
	ca	co	OR (95% CI)	ca	co	OR (95% CI)
Personal history						
Overall	6	24	0.5 (0.2-1.1)	58	109	1.0 (0.7-1.4)
Age at diabetes						
<30 years at diabetes	5	19	0.5 (0.2-1.4)	0	1	0.0 (0.0-∞)
30+ years at diabetes	1	5	0.3 (0.0-2.7)	58	108	1.0 (0.7-1.4)
Family history						
Overall	251	640	0.7 (0.6-0.8)	149	266	1.0 (0.8-1.3)
Age at diabetes						
<30 years at diabetes	20	51	0.7 (0.4-1.3)	18	32	1.0 (0.6-1.8)
30+ years at diabetes	233	596	0.7 (0.6-0.8)	132	237	1.0 (0.8-1.3)
Type of Relative						
Parent	216	553	0.7 (0.6-0.8)	72	93	1.5 (1.1-2.2)
Sibling	23	81	0.5 (0.4-0.9)	8	14	1.0 (0.4-2.3)
Offspring	18	29	1.1 (0.6-2.0)	74	162	0.9 (0.7-1.1)

[1]Data stratified by age at diabetes and by age at HL.–[2]Numbers denote included numbers of cases and controls.

among their family members, is scarce as available reports have not specifically investigated HL.[10,24,25] In our study, we observed inverse associations with young-adult-onset HL amounting to a nonstatistically significant but consistent 50% reduced risk associated with a personal history of diabetes mellitus type I, a 30% reduced risk associated with any family history of diabetes mellitus and a 50% reduced occurrence of diabetes mellitus in siblings of cases with young-adult onset HL. The inverse association with family history, which was independent of personal history, suggests that the nature of the association between diabetes mellitus type I and young-adult-onset HL is not exclusively mediated by intra-individual factors (e.g., intra-uterine or peri-natal environment, or birth order) but open the possibility that genetic factors that increase susceptibility to diabetes act to decrease susceptibility to HL.

We used a register-based case-control design, which ruled out recall-bias, ensured a population-based setting, and generalisability of our findings. Validations of the routine diagnoses of HL within the framework of other studies suggest a higher than 90% validity during the 1990s (the remainder chiefly being made up by misclassification of NHL in older adults as HL).[26,27] Misclassification of outcome (HL) is thus an unlikely explanation for our findings, as these remained largely similar in analyses restricted to the period 1990–2000. Although all patients with type II diabetes mellitus may not ever be treated in inpatient care, the exposure of interest (classical type I diabetes mellitus of autoimmune origin) is always treated on an inpatient basis at the time of onset of disease. We used an upper age limit of 30 years of age at first diabetes mellitus discharge to defined diabetes mellitus type I, since in Sweden, other types than autoimmune (type I) is exceedingly rare before 30 years of age (particularly so during the study period 1964–2000). Importantly, different age-cutoffs either improved (<40 years at first discharge) or decreased (<20 years at first discharge) statistical precision but resulted in closely similar risk estimates (data not shown). In any case, any erroneous inclusion of diabetes mellitus type II would likely dilute our risk estimates, and are thus unlikely to explain the observed reduced risks. Moreover, the prevalence of a diabetes mellitus discharge among the controls of young adult onset HL (0.5% overall, 0.4% when defined as diabetes before 30 years of age and 0.3% when defined as before 20 years of age) corresponds well with the estimated prevalence of diabetes mellitus type I in the general population.[14] The observed inverse association between young-adult-onset HL and diabetes mellitus therefore at least applies to type I diabetes mellitus. The observed increased risk of diabetes mellitus among parents (who all were diagnosed above the age of 30 years) and late onset HL may be a chance finding. Since HL in older adults does not share epidemiological characteristics with young-adult-onset HL[1,28] and since in Sweden diabetes mellitus above 30 years of age reflects mix of type I and type II diabetes mellitus dominated by the latter as age increases, the observed association may be biologically different from the inverse association observed between diabetes mellitus type I and young-adult-onset HL.

Limitations of our study include lack of information on potential confounders (although the matched design and analyses ensured adjustment for sex, age, geography and marital status), the lack of validation of the register-based data used to define exposure and outcome and lack of data on, *e.g.*, EBV-status of the HL tumors. The observed increased risk of diabetes mellitus among parents (whose earliest dates of discharges were all at ages above 30 years) and late onset HL is less easily interpreted. Accordingly, inherent in the time restraints/constraints imposed by the used registers not all HL patients older than 45 years nor their siblings and parents were at risk of DM discharge before the age of 30 years, implying as mentioned that the observed cases of DM in these group of relatives comprise a mix of prevalent cases of type I DM and incident cases of type II DM. With these precautions, however, HL in older adults differ epidemiologically from young-adult-onset HL[1,27] and the observed association may be biologically different from the inverse association observed between diabetes mellitus type I and young-adult-onset HL.

Our findings add to previous indications of a possible link between autoimmunity and susceptibility to young-adult HL,[9,11,12,29] which might provide important insights into the yet unknown pathologies of both young-adult HL and autoimmunity, both of which appears to involve a dysregulated host response against infectious agents.

In conclusion, immune characteristics associated with susceptibility to autoimmune diseases like diabetes mellitus type I may be of importance in the pathogenesis of young-adult-onset HL.

References

1. MacMahon B. Epidemiology of Hodgkin's disease. Cancer Res 1966;26:1189–201.
2. Hjalgrim H, Askling J, Rostgaard K, Hamilton-Dutoit S, Frisch M, Zhang JS, Madsen M, Rosdahl N, Konradsen HB, Storm HH, Melbye M. Characteristics of Hodgkin's lymphoma after infectious mononucleosis. N Engl J Med 2003;349:1324–32.
3. Evans AS, Gutensohn NM. A population-based case-control study of EBV and other viral antibodies among persons with Hodgkin's disease and their siblings. Int J Cancer 1984;34:149–57.
4. Axdorph U, Porwit-MacDonald A, Sjoberg J, Grimfors G, Ekman M, Wang W, Biberfeld P, Bjorkholm M. Epstein-Barr virus expression in Hodgkin's disease in relation to patient characteristics, serum factors and blood lymphocyte function. Br J Cancer 1999;81:1182–7.
5. Goldin LR, Pfeiffer RM, Gridley G, Gail MH, Li X, Mellemkjaer L, Olsen JH, Hemminki K, Linet MS. Familial aggregation of Hodgkin lymphoma and related tumors. Cancer 2004;100:1902–8.
6. Mack TM, Cozen W, Shibata DK, Weiss LM, Nathwani BN, Hernandez AM, Taylor CR, Hamilton AS, Deapen DM, Rappaport EB. Concordance for Hodgkin's disease in identical twins suggesting genetic susceptibility to the young-adult form of the disease. N Engl J Med 1995;332:413–8.
7. Alexander FE, Jarrett RF, Cartwright RA, Armstrong AA, Gokhale DA, Kane E, Gray D, Lawrence DJ, Taylor GM. Epstein-Barr Virus and HLA-DPB1-*0301 in young adult Hodgkin's disease: evidence for inherited susceptibility to Epstein-Barr Virus in cases that are EBV(+ve). Cancer Epidemiol Biomarkers Prev 2001; 10:705–9.
8. Cimino G, Lo Coco F, Cartoni C, Gallerano T, Luciani M, Lopez M, De Rossi G. Immune-deficiency in Hodgkin's disease (HD): a study of patients and healthy relatives in families with multiple cases. Eur J Cancer Clin Oncol 1988;24:1595–601.
9. Mellemkjaer L, Andersen V, Linet MS, Gridley G, Hoover R, Olsen JH. Non-Hodgkin's lymphoma and other cancers among a cohort of patients with systemic lupus erythematosus. Arthritis Rheum 1997; 40:761–8.
10. Mellemkjaer L, Alexander F, Olsen JH. Cancer among children of parents with autoimmune diseases. Br J Cancer 2000;82:1353–7.
11. Gridley G, McLaughlin JK, Ekbom A, Klareskog L, Adami HO, Hacker DG, Hoover R, Fraumeni JF, Jr. Incidence of cancer among patients with rheumatoid arthritis. J Natl Cancer Inst 1993; 85:307–11.
12. Ekstrom K, Hjalgrim H, Brandt L, Baecklund E, Klareskog L, Ekbom A, Askling J. Risk of malignant lymphomas in patients with rheumatoid arthritis and in their first-degree relatives. Arthritis Rheum 2003; 48:963–70.
13. Mattsson B, Wallgren A. Completeness of the Swedish Cancer Register. Non-notified cancer cases recorded on death certificates in 1978. Acta Radiol Oncol 1984;23:305–13.
14. Anonymous, Patientregistret 1987–1996: Kvalitet och innehåll (Swedish). EpC, National Board of Health and Welfare, 1998.
15. Skarle A. Flergenerationsregistret. Statistics Sweden, Population Statistics, 2001.
16. Dahlquist G, Blom L, Tuvemo T, Nystrom L, Sandstrom A, Wall S. The Swedish childhood diabetes study: results from a nine year case register and a one year case-referent study indicating that type 1 (insulin-dependent) diabetes mellitus is associated with both type 2 (non-insulin-dependent) diabetes mellitus and autoimmune disorders. Diabetologia 1989;32:2–6.
17. Dahlquist G, Blom L, Lonnberg G. The Swedish Childhood Diabetes Study: a multivariate analysis of risk determinants for diabetes in different age groups. Diabetologia 1991;34:757–62.

18. Bodansky HJ, Staines A, Stephenson C, Haigh D, Cartwright R. Evidence for an environmental effect in the aetiology of insulin dependent diabetes in a transmigratory population. Br Med J 1992; 304:1020–2.
19. Bingley PJ, Douek IF, Rogers CA, Gale EA. Influence of maternal age at delivery and birth order on risk of type 1 diabetes in childhood: prospective population based family study: Bart's-Oxford Family Study Group. BMJ 2000;321:420–4.
20. Chang ET, Zheng T, Weir EG, Borowitz M, Mann RB, Spiegelman D, Mueller NE. Childhood social environment and Hodgkin's lymphoma: new findings from a population-based case-control study. Cancer Epidemiol Biomarkers Prev 2004;13:1361–70.
21. Wilson SB, Kent SC, Patton KT, Orban T, Jackson RA, Exley M, Porcelli S, Schatz DA, Atkinson MA, Balk SP, Strominger JL, Hafler DA. Extreme Th1 bias of invariant Valpha24JalphaQ T cells in type 1 diabetes. Nature 1998;391:177–81.
22. Anonymous. Infections and vaccinations as risk factors for childhood type I (insulin-dependent) diabetes mellitus: a multicentre case-control investigation.EURODIAB Substudy 2 Study Group. Diabetologia 2000;43:47–53.
23. Westergaard T, Melbye M, Pedersen JB, Frisch M, Olsen JH, Andersen PK. Birth order, sibship size and risk of Hodgkin's disease in children and young adults: a population-based study of 31 million person-years. Int J Cancer 1997;72:977–81.
24. Hjalgrim H, Frisch M, Ekbom A, Kyvik KO, Melbye M, Green A. Cancer and diabetes: a follow-up study of two population-based cohorts of diabetic patients. J Intern Med 1997;241:471–5.
25. Zendehdel K, Nyren O, Ostenson CG, Adami HO, Ekbom A, Ye W. Cancer incidence in patients with type 1 diabetes mellitus: a population-based cohort study in Sweden. J Natl Cancer Inst 2003;95:1797–800.
26. Axdorph U, Porwit-Macdonald A, Sjoberg J, Grimfors G, Bjorkholm M. T-cell-rich B-cell lymphoma: diagnostic and therapeutic aspects. Apmis 2002;110:379–90.
27. Smedby KE, Akerman M, Hildebrand H, Glimelius B, Ekbom A, Askling J. Malignant lymphomas in coeliac disease: evidence of increased risks for lymphoma types other than enteropathy-type T cell lymphoma. Gut 2005;54:54–9.
28. Alexander FE, McKinney PA, Williams J, Ricketts TJ, Cartwright RA. Epidemiological evidence for the ''two-disease hypothesis'' in Hodgkin's disease. Int J Epidemiol 1991;20:354–61.
29. Mellemkjaer L, Linet MS, Gridley G, Frisch M, Moller H, Olsen JH. Rheumatoid arthritis and cancer risk. Eur J Cancer 1996;32A: 1753–7.